REMARKS/ARGUMENTS

Claim Rejections

Rejections under 35 U.S.C. § 103

The Office has rejected pending claims 1-2, 5-6 and 9-10 as allegedly being unpatentable over Ghirri et al. (US6352974) in view of Bay et al. (US20020065255). The Office alleges that Ghirri provides all the elements of the pending claims but concedes that "Ghirri does not teach an oral calcitonin pharmaceutical composition comprising a delivery agent selected from the group consisting of 5-CNAC, SNAD, SNAC, and said delivery agent is disodium salt thereof." (Office Action at p. 6). However, the Office alleges that Bay teaches "pharmaceutical compositions comprising a delivery agent, which is a disodium salt of 5-CNAC, SNAD, or SNAC, and an active agent, such as salmon calcitonin." (*Id.*). The Office concludes that it would have been obvious to combine the teachings of Ghirri with those of Bay, because Bay teaches that the disodium salt of 5-CNAC, SNAD, or SNAC can increase efficacy for delivering the active agent. (*Id.* at pp. 6-7).

In the Advisory Action mailed June 24, 2009, the Office alleges that Ghirri's use of the phrase "up to" (in relating to calcitonin activity), allows the unit dose of a Ghirri composition to meet Applicants' previously recited range of between 0.4 and 2.5 mg (the claims now recite does of 0.4 - 1.2 mg, 0.8 – 1.2 mg or about 1 mg). The Office also alleges that even though Bay suggests that a very large calcitonin dose is required when it is used in combination with 5-CNAC, Ghirri teaches therapeutically effective doses of calcitonin and Ghirri does not require high doses of calcitonin. The Office also alleges that the Final Office action provided sufficient evidence that a calcitonin could be successfully used to treat osteoarthritis.

For the following reasons, that rejection is respectfully traversed.

I. Obviousness Standards

Graham v. John Deere Co. of Kansas City, 383 U. S. 1, 17-18 (1966), establishes an objective analysis for applying §103 to a question of obviousness: "the scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved." The United States Patent and Trademark Office bears the burden of establishing a prima facie case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case generally requires three showings: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; 2) a reasonable expectation of success; and 3) that the prior art reference or combination of references teaches or suggests all the claim limitations. MPEP §2143.

The United States Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case requires three showings:

1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings;

2) a reasonable expectation of success; and

3) that the prior art reference or combination of references teaches or suggests all the claim limitations.

In the present application, the results of the factual inquiries under *Graham* do not support a *prima facie* case that the pending claims are obvious under 35 U.S.C. §103(a).

II. Failure to Support a *Prima Facie* Case

a. The Combination of Ghirri and Bay Neither Discloses Nor Suggests The Subject Matter of Applicants' Claims

All claims currently recite dosages of either 0.4 – 1.2 mg, 0.8 - 1.2 mg, or about 1 mg of calcitonin.

For the first factual inquiry under *Graham*, i.e., the determination of the scope and content of the prior art, the Office is required to consider what the prior art as a whole teaches. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention). The MPEP specifically requires the Office to "consider[] both the invention and the prior art references as a whole." MPEP § 2141.02. Applicants respectfully submit that the Office has not considered the entirety of what the art at a whole teaches.

Bay provides a very large dose of 800 µg salmon calcitonin to monkeys (Example 4) and 25 mg/kg – 4000 mg/kg salmon calcitonin to rats in order to orally deliver salmon calcitonin and achieve the salmon calcitonin serum concentrations shown in Bay's Examples. Therefore, Bay teaches that a very large dose of salmon calcitonin is required in combination with, e.g., 5-CNAC to achieve pharmaceutically acceptable levels of salmon calcitonin *in vivo* when said calcitonin is delivered orally. This is in accord with what is understood by skilled artisans regarding oral delivery of proteins, as peptides and proteins are known to be degraded by stomach acids, resulting in poor bioavailabilty. In contrast to what is generally understood by skilled artisans and what Bay explicitly teaches, Applicants' methods require *only* between 0.4 - 1.2 mg, 0.8 – 1.2 mg or about 1 mg of salmon calcitonin in free or salt form when salmon

calcitonin is used in combination with the recited delivery agents. This directly contradicts the teachings of Bay. Accordingly, taken as a whole, Bay teaches away from using the doses recited in Applicant's claimed methods. Teaching away from a claimed invention amounts essentially to a *per se* demonstration of lack of prima facie obviousness. *In re Dow Chemical Col*, 837 F.2d 469, 472 (Fed. Cir. 1988); *In re Fine*, 837 F.2d 1071, 1073-74 (Fed. Cir. 1988).

The Office argues that, while Bay teaches a large dose of calcitonin, Ghirri does not teach a large dose calcitonin. But the Office ignores that Ghirri does not use 5-CNAC, SNAD or SNAC in any composition therein, and therefore Ghirri cannot teach a dose of calcitonin that one would use when one delivers calcitonin via 5-CNAC, SNAD or SNAC. In contrast, Bay teaches amounts of calcitonin that one might use for oral delivery when using 5-CNAC, SNAD or SNAC, and Bay very clearly teaches that the amount is very large. When an artisan analyzes the art cited by the Office, that artisan would understood that various doses of calcitonin may be formulated into a pharmaceutical composition, but if the oral delivery agent chosen is 5-CNAC, SNAD, or SNAC, then the amount of calcitonin required is very high. The Office may not simply ignore what Bay teaches regarding the relationship of 5-CNAC, SNAD, or SNAC and calcitonin amount – as the question for any obviousness analysis is what does the art as a whole teach or suggest?

For at least this reason, Applicants respectfully request withdrawal of the outstanding obviousness rejections.

Even if one were to ignore the explicit teachings of Bay, which teaches that oral delivery of calcitonin with carriers such as 5-CNAC requires a very large amount of calcitonin, there is no reason that one would specifically select 0.4 - 1.2 mg, 0.8 – 1.2 mg, and especially not about 1 mg calcitonin, from the vast dosage ranges described in Bay and Ghirri. 2144.05 of the MPEP states that when dealing with ranges in a claim:

> if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. Id. See also In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08.

Applicants respectfully submit that the ranges disclosed in Bay and Ghirri are very broad, such that traditional genus species law is invoked. Bay provides a dose of 800 µg to a monkey (average rhesus monkey weight is in the order of about 5 kg), which translates to a human dose of about 11 mg (assuming an average human weight of 70 kg).[1] Bay doses rats with compositions having 25 mg/kg – 4000 mg/kg calcitonin, which translates to a human dose of

[1] This assumes that one could simply derive a human calcitonin dose from a monkey dose and is used for illustration only.

1.75 g -280 g.[2] Together the rat and monkey doses of Bay provide a human dosage range of 11 mg – 280 g. This is a very broad range. Regarding Ghirri, the Office argues that the Ghirri range overlaps with Applicants' range because the calcitonin in Ghirri can have an activity of "up to" 6,500 IU/mg. If this is so, then Ghirri discloses a dosage range of 3 µg - 598 mg (assuming "up to" means 1-6,500 IU/mg). This is a tremendously broad range. Together, Ghirri and Bay provide a dosage range of 3 µg -280 g, which is an enormous range of potential doses.

To establish a *prima facie* case of obviousness in a genus-species situation, a motivation must be shown for the skilled artisan to make the claimed invention as a whole, i.e., to select the relevant species from a disclosed prior art genus.[3] *See* MPEP §2144.08. Thus, for the amended claims, the Office must rationally articulate some apparent reason or provide some explicit motivation to specifically choose a calcitonin dosage of 0.4 – 1.2 mg (for claim 1), 0.8 to 1.2 mg (for claims 24 and 30), and about 1 mg (for claims 27 and 33) from the enormous dosage range of Bay and Ghirri, and to then combine that amount of calcitonin with 5-CNAC, SNAD or SNAC in an oral composition for treating osteoarthritis. MPEP §2141.02 warns of distilling an invention down to a "gist" or "thrust", as such distillation disregards the "as a whole" requirement for an obviousness analysis. *See W.L. Gore*, 721 F.2d 1540 (Fed. Cir. 1983). Given that genus species law applies, it is not sufficient to merely identify an alleged motivation to select a dose in general; rather what must be shown is some motivation to select the doses recited in Applicants' claims.

The Office has not articulated any apparent reason that a skilled artisan would select a dosage from 0.4 - 1.2 mg, 0.8 – 1.2 mg, or about 1 mg. In the absence of an articulated reason with rational underpinnings, the Office can only be said to have used hindsight based on Applicants' own disclosure to identify Applicants' recited doses. Such hindsight reasoning is impermissible. *Texas Instruments Inc. v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). On this point, the Board of Patent Appeals and Interferences recently reversed an Examiner's rejections based on obviousness, by clarifying that

> The U.S. Supreme Court recently held that rigid and mandatory application of the "teaching-suggestion-motivation," or TSM, test is incompatible with its precedents. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007). The Court did not, however, discard the TSM test completely; it noted that its precedents show that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id.

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[2] This assumes that one could simply derive a human calcitonin dose from a rat dose and is used for illustration only.

[3] For a genus-species situation, an obviousness inquiry requires the Office to consider the size of the genus, the express teachings of the art, the teachings of structural similarity, similar properties, and predictability of the technology. MPEP §2144.08.

Ex Parte Whalen II, Appeal 2007-4423, July 23, 2008 (emphasis added).

At best, the Office is arguing that the dosage range may be obvious to try. However, the KSR holding by the Supreme Court suggests that if there are not a finite number of solutions to a problem, or if such solutions are not predictable, or if success is not anticipated, then a claimed invention is not obvious without some additional showing by the Office. *See KSR International Co.*, 127 S. Ct. at 1742 (2007); *accord Ortho McNeil Pharm. Inc. v Mylan Labs*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Applicants respectfully submit that, as evidenced by various publications available at the time the instant application was filed (which were discussed in the previously-filed Amendment and Response, and which are discussed below), success was not even anticipated for the use of calcitonin in humans, less so the use of oral calcitonin, and even less so the specific oral calcitonin doses recited in Applicants' claims. Thus, "obvious to try", which appears to be the Office's rationale for obviousness, is not appropriate in the instant situation. *See id; accord In re Kubin*, 561 F.3d 1351, (Fed. Cir. 2009) (discussing the Supreme Court's analysis of "obvious to try", which limits its application to situations having a "finite number of identified, predictable solution" or when "the improvement is [no] more than the predictable use of prior art elements according to their established functions."); accord *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Even if Bay did not teach away from Applicants' claims, and the range of Bay and Ghirri is not large enough to require traditional genus species analysis, as evidenced by Applicants' results on page 26, human dosing of calcitonin in combination with 5-CNAC yields unpredictable results that prohibits simple optimization of a prior art dose. Namely, in human clinical trials, the 1.0 mg dose shows benefit (-19.7 %) over the 0.4 mg dose (-15.12%), while the 2.5 mg dose does not show benefit (-17.5%) over the 1.0 mg dose. There is not a simple linear relationship between a dose of calcitonin in combination with 5-CNAC and a reduction of osteoarthritis in humans. Thus, it cannot be fairly said that Applicants' dose may be arrived at via routine optimization, in which a skilled artisan might extrapolate a prior art rat or monkey dose to arrive a clinically effective human dose.

b. The Combination of Ghirri and Bay Does Not Provide a Reasonable Expectation of Success at Arriving at Applicants' Claims

A *prima facie* case of obviousness must also establish that there is a reasonable expectation of success at arriving at Applicants' claimed subject matter upon combining Ghirri and Bay. *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). However, in the instant situation, the asserted combination of Ghirri and Bay does not provide a reasonable expectation of success at arriving at Applicants' claims.

First, it must be understood that oral delivery of proteins is extremely difficult to achieve, and hence extremely unpredictable. Indeed Ghirri admits as much at column 3, stating:

> Although solid oral dosage forms are desirable, their provision is not always possible. In the case of polypeptides such as calcitonins the provision of solid oral dosage formulations is hindered by the high instability of the polypeptides. These materials are not suitable for processing into a solid dosage forms because they cannot withstand the physical and chemical stresses of conventional formulating techniques. There is therefore a need for calcitonin in a solid dosage form, more particularly there is a need for a solid oral dosage form of calcitonin. There is a further need for calcitonin in a solid dosage form with an improved shelf life, more preferably one which will not have to be stored at low temperatures.

The Office may not simply ignore this explicit teaching of unpredictability found in the cited art. Moreover, oral delivery of peptides faces additional hurdles not mentioned in Ghirri, i.e., circumventing the natural degradation and digestion of proteins in the gut of an intended patient, and poor bioavailability and absorption. Simply put, oral delivery of polypeptides is extremely difficult and therefore the expectation of success is quite low.

Second, neither Ghirri nor Bay provide any evidence that salmon calcitonin may be successfully used to treat osteoarthritis.

Ghirri merely states:

> Calcitonins are hypocalcemic hormones found in the thyroid, parathyroid and thymus glands of man and in separate organs called ultimobranchial bodies in non-mammalian vertebrates. During hypercalcemia calcitonins reduce elevated plasma calcium concentration to normal levels by inhibiting bone resorption. Calcitonins are therefore used to treat a variety of conditions such as Paget's disease, post menopausal osteoporosis and also to treat hypocalcemia resulting from vitamin D intoxication, neoplastic disease, thyrotoxicosis or hyperthyroidism.

(Column 2). However, Ghirri provides no data to substantiate this assertion. That is, while Ghirri prepares certain oral calcitonin formulations, Ghirri provides no evidence that these formulations (or any calcitonin formulation) could be successfully used to treat osteoarthritis. In fact, Ghirri does not administer a single composition to an animal or test a single composition in any *in vitro* model. Thus, Ghirri provides NO evidence that one may use salmon calcitonin to treat osteoarthritis. Ghirri, at best, provides a wish, which is not legally sufficient to be considered enabling art – particularly in a field as unpredictable as the treatment of arthritis.

This deficiency in the Office's primary reference is not supplemented by the disclosure of Bay. While Bay formulates salmon calcitonin with, e.g., 5-CNAC, and delivers this composition to rats and monkeys, Bay provides NO evidence that these compositions (or any other salmon calcitonin composition) would result in what Applicants claim, i.e., <u>treating</u> osteoarthritis. That is, Bay's successful <u>delivery</u> of salmon calcitonin to a rat or a monkey tells nothing about whether that delivery (and dose) actually results in treatment of the rat or monkey, and certainly tells nothing about whether salmon calcitonin would actually result in treatment of a human.

The present application demonstrates for the first time that calcitonin: 1) can be orally delivered in combination with 5-CNAC, SNAD or SNAC to humans; and 2) is efficacious in the treatment of osteoarthritis in humans, as measured by suitable biomarkers of cartilage degradation. The present application discloses that oral delivery of salmon calcitonin is superior for suppression of cartilage degradation in humans and thereby superior for treatment and prevention of osteoarthritis. In contrast, the cited references do not demonstrate that a combination of, e.g., 5-CNAC and salmon calcitonin is effective in treating osteoarthritis in humans (or preserving or stimulating cartilage etc.).

The present specification states on page 1 that, at the time of filing the instant application, no study had shown calcitonin to be effective in treating osteoarthritis in humans. Indeed, the specification makes clear on page 1 that conflicting reports existed at the time of filing as to whether calcitonin could even be used to prevent cartilage destruction. Moreover, it is known to be difficult to translate a drug-induced structural effect (like cartilage erosion) in an animal model of osteoarthritis into an expectation of efficacy in human osteoarthritis. For example, Manicourt et al., 1999 (submitted herewith as part of an IDS) shows that daily subcutaneous injections of salmon calcitonin in 2-4 years old mongrel dogs with anterior cruciate ligament transection (ACLT) caused a significant reduction in the grade and size of cartilage erosion compared to placebo. However, Hayami et al., 2004 (submitted herewith as part of an IDS) shows that bisphosphonates significantly and dose-dependently reduced the Mankin score in a rodent ACLT model, whereas subsequent bisphosphonate clinical studies in humans failed to demonstrate any beneficial effects on clinically relevant osteoarthritis endpoints (Bingham et al., 2006 (submitted herewith as part of an IDS)). In addition, a recent phase III clinical study of the MMP-inhibitor PG-116800 failed to demonstrate any beneficial effects in patients with knee osteoarthritis, regardless of its apparent success in animals. Indeed, as of this date, more than 20 anti-rheumatic MMP-inhibitor drug development programs have been discontinued; thus, positive preclinical indications for arthritis treatment (e.g., animal models) have failed over a broad range of compounds to translate into human efficacy in treating arthritis and joint disease.

Negative outcomes of human arthritis trials with bisphosphonates, MMP-inhibitors and other compounds exemplify the unpredictable nature of extrapolating animal models to the treatment of human arthritis. Prior to Applicants' invention, one does not find disclosures that suggest that using calcitonin would have a reasonable expectation of success for the treatment of patients with osteoarthritis. There is significant evidence of unpredictability in the osteoarthritis field in general, and with calcitonin-based treatments in particular, that cannot be ignored in evaluating what the art as a whole teaches, the underlying question asked for any obviousness analysis.

In summary, there is unpredictability in:

- the use of calcitonin to treat osteoarthritis in any animal (including humans);
- attempting to orally deliver proteins;
- the bioavailability of an orally administered calcitonin in a human (e.g., what is the required calcitonin peak serum concentration for human treatment?); and
- the dosages of calcitonin required for treating osteoarthritis in humans (e.g., see the extremely high doses disclosed in the Bay and the vast range of potential dose found in Ghirri).

In spite of the unpredictability above, Applicants invested in, tested, and identified particular doses of calcitonin in combination with 5-CNAC, SNAD, SNAC or disodium salts thereof that may be used to successfully treat osteoarthritis in humans. This success was measured by markers of cartilage degradation in the urine of treated patients, which undeniably evidences a decrease in cartilage loss. In contrast, there is nothing in Ghirri or Bay, separately or in combination, suggesting that: 1) salmon calcitonin can be used to effectively treat osteoarthritis in a human; 2) salmon calcitonin can be orally delivered to a human using 5-CNAC, SNAD, SNAC or disodium salts thereof; and 3) upon oral delivery of 0.4 - 1.2 mg, 0.8 - 1.2 mg or about 1 mg of salmon calcitonin in free or salt form formulated with 5-CNAC, SNAD, SNAC or disodium salts thereof, one can achieve therapeutic levels of salmon calcitonin in a human.[4] The combination of Ghirri and Bay provides no evidence (less so a reasonable expectation) that such highly desirable results may be obtained. Accordingly, Applicants assert that even if, *arguendo*, the Office could maintain that one would be motivated to combine Ghirri and Bay, this combination does not render obvious Applicants' instant claims, because there is no reasonable expectation of success at achieving Applicants' currently claimed methods.

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[4] To be applicable as prior art, the combination of applied references must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). An enabling disclosure requires the public to be in possession of a claimed invention before the date of invention. Such possession is effected if the reference teachings could have been combined with the knowledge of one of ordinary skill in the art, to make the claimed invention. *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). To constitute a publication, an invention must be described sufficiently to impart to a person with ordinary skill and knowledge of the prior art the information needed to devise the invention without further genuine inspiration or undue experimentation. *Regents of U. Cal v. Howmedica, Inc.*, 210 USPQ 727, 738 (DNJ 1981); see also *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (stating "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1471 (Fed. Cir. 1997); *In re Payne*, 606 F.2d 303, 314 (CCPA 1979). As discussed above, the combined teachings of Ghirri and Bay do not meet the standard of an enabling disclosure.

c. Applicants' Claimed Methods Display Unexpectedly Beneficial Results

Assuming *arguendo*, that the Office has established a prima facie case of obviousness, he results provided for Applicants' methods rebuts any *prima facie* case of obviousness. (See MPEP 716.02(d) stating "To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range."). All claims currently recite treatment of osteoarthritis with dosages of either 0.4 – 1.2 mg, 0.8 - 1.2 mg, or about 1 mg of calcitonin. As evidenced by Applicants' results on page 26, these cited ranges provide unexpectedly beneficial results. In human clinical trials, the 1.0 mg dose shows benefit in reducing urinary CTX-1 at 3-month treatment (-19.7%) over the 0.4 mg dose (-15.12%), while the 2.5 mg dose did not show benefit (-17.5%) over the 1.0 mg dose.. Moreover, page 26 discloses that women receiving 1.0 mg of calcitonin with 5-CNAC had the greatest reduction in 24-hour urinary CTX-1 compared to placebo. For CTX-II reduction, women who received 1.0 mg of calcitionin with 5-CNAC and were in the highest cartilage turnover at baseline had the greatest decrease in urinary CTX-II after 3-month treatment (compared to women in the lowest tertile). A similar trend was seen for the 0.4 mg dose. Further, aside from the clinical benefits seen with lower doses of calcitonin and 5-CNAC, e.g., 0.4 mg and 1 mg, a lower dose range is highly desireable because it decrease costs and the likelihood of adverse events.

There is absolutely nothing in Bay or Ghirri, separately or in combination, that suggests such dramatic and highly desirable results with 0.4 – 1.2 mg, 0.8 - 1.2 mg, or about 1 mg of calcitonin in combination with 5-CNAC, SNAD, SNAC or disodium salts thereof. Accordingly, Applicants assert that even if, *arguendo*, the Office could maintain that the combination of Bay and Ghirri renders obvious Applicants' instant methods, such surprising and/or unexpected results rebut any *prima facie* case of obviousness. *See* MPEP §2144.09 (*citing In re Papesch*, 315 F.2d 381 (CCPA 1963)). Furthermore, there is no reasonable expectation from Bay and Ghirri of similar properties, which is further demonstrated by Applicants' surprising results. *See* MPEP §2144.09.

III. Summary

Based on the evidence as a whole, the combination of Ghirri and Bay does not support a finding of *prima facie* obvious. *See* MPEP § 2144.08; *In re Bell*, 991 F.2d 781,784 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)). The Office has not shown any motivation or apparent reason to select Applicants' claimed dose ranges from the tremendous range of doses found in the cited art, nor has the Office shown a reasonable expectation of

success at achieving Applicants' claimed subject matter.[5] In the present application, the results of the factual inquiries under Graham do not support that the pending claims are *prima facie* obvious under 35 U.S.C. §103(a). Moreover, Applicants respectfully submit that any *prima facie* case has been successfully rebutted and overcome. Accordingly, Applicants respectfully request withdrawal of the obviousness-based rejection of the pending claims.

Double Patenting

Pending claim 2 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 9 and 10 of copending Application No. 11/577,127.

Pending claims 1-2 and 10 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 13-15 of copending Application No. 12/132,642.

Pending claims 1-2 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 26, 28 and 29 of copending Application No. 12/093,383.

The present application is further along in prosecution than the above-identified co-pending applications. Applicants therefore respectfully request that upon allowance of the claims under consideration in this application, the Office withdraw the double patenting rejection in this application, and make a provisional double patenting rejection in the above-identified co-pending applications. The provisional rejection in the above-identified co-pending applications may then be converted into a double patenting rejection upon the present application issuing into a patent. See MPEP 804.

[5] Applicants also do not concede that there is sufficient motivation to combine Ghirri and Bay. However, it is not necessary for Applicants to detail those arguments at this time, given that the Office has not established the other *Graham* factors.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080
(862) 778-9308
Date: 7/27/07

Leslie Fischer
Attorney for Applicants
Reg. No. 58,393